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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,604	07/01/2003	Wei Huang	011068-014-999	4803

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
05/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,604	HUANG ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed February 7, 2008 is acknowledged and entered. Claims 1-19 remain pending and under examination. This Office action is made non-final in view of the reinstated ground of rejection. Any inconvenience is regretted.

Response to Amendment

2. The following objections and rejection are withdrawn:

- The objections to claims 1-4, 7 and 10-19 are withdrawn in view of Applicant's amendment.
- The rejection of claims 1-4, 10 and 15-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter) for the recitation of "226" is withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nijhuis *et al.* (*Current Opinion in Infectious Diseases*, 2001, 14:23-28, "Nijhuis") in view of Whitcomb (WO 99/61658). The claims are drawn to a method for determining whether an HIV-1 virus has an increased likelihood of having an impaired replication capacity. Critical to understanding the

scope of the subject matter claimed is the following definition offered in the specification, page 10, lines 25-34:

> A virus has an "increased likelihood of having impaired replication capacity" if the virus has a property, for example, a mutation, that is correlated with an impaired replication capacity. A property of a virus is correlated with an impaired replication capacity if a population of viruses having the property has, on average, an impaired replication capacity relative to that of an otherwise similar population of viruses lacking the property. Thus, the correlation between the presence of the property and impaired replication capacity need not be absolute, nor is there a requirement that the property is necessary (*i.e.*, that the property plays a causal role in impairing replication capacity) or sufficient (*i.e.*, that the presence of the property alone is sufficient) for impairing replication capacity.

Given the definition in the specification, an increased likelihood of having impaired replication capacity is reasonably considered a loose association between a particular property and impaired replication capacity since the presence of the property and resulting impaired replication capacity need not be absolute, not necessary and not sufficient.

The method steps comprise: detecting whether the reverse transcriptase (RT) encoded by said HIV-1 exhibits the presence or absence of a mutation associated with impaired replication capacity. The mutation occurs at position 98, 100, 101, 103 106, 108, 179, 181, 188, 190, 225 or 236 (not mutation P236L) in said reverse transcriptase. Specific substitution mutations are A98G, L100I, K101E, K103N, V106A, V106I, V106M, Y181C, Y188A, Y188C, Y188H, Y188L, G190A, G190C, G190E, G190T, G190V, G190Q, G190S, G190V, P236L and P225H. The mutation confers resistance to a non-nucleoside reverse transcriptase inhibitor, such as nevirapine, delavirdine or efavirenz. Also claimed is a method for determining whether a subject has an HIV-1 with an increased likelihood of having an impaired replication capacity. The

subject is undergoing or has undergone prior treatment with an antiviral drug. Also claimed are combinations of mutations that include P236L and K103N.

Nijhuis discloses the implications of antiretroviral resistance on viral fitness. Viral fitness is a synonym for replication capacity (page 23, introduction section). *In-vivo* drug resistance mutations on replication potential for HIV-1 in the presence of non-nucleoside reverse transcriptase inhibitors such as delavirdine include 103N (see Table 1, page 24, and page 25, first column, second full paragraph). Nijhuis teaches that the K103N mutation has a reducing effect on replicative capacity. Nijhuis also discloses that P236L is a NNRTI *in vivo* mutation that reduces replication capacity (Table 1).

Nijhuis is silent on mutations of more than three positions relating to NNRTIs and some of the combinations instantly claimed that involve mutations other than or in addition to K103N and P236L.

However, Whitcomb discloses means and methods for monitoring non-nucleoside reverse transcriptase inhibitor anti-retroviral therapy, specifically HIV therapy (abstract). Whitcomb discloses substitution mutations in HIV-1 reverse transcriptase at codons 101, 103 and/or 109 that correlate with changes in delavirdine, nevirapine and efavirenz susceptibility (page 12, lines 4-25). Also taught is that mutations at codons 106, 189, 181 and/or 227 of HIV-1 reverse transcriptase result in decreased susceptibility to delavirdine, nevirapine and efavirenz (pages 14-16). Another embodiment of Whitcomb's invention is that a mutation at codon 190 (G190A) either alone or in combination with a mutation at codon 130 (K103N) of HIV-1 RT correlates with resistance to antiretroviral therapy (page 14, lines 29-34). Another embodiment of Whitcomb's invention is that a mutation at codon 236 (P236L) either alone or in combination

with mutations at other codons including 103 (K103N) and/or 181 (Y181C) of HIV RT correlates with resistance to antiretroviral therapy (see description of figures 5 and 6, pages 22-23). Other mutations include 98, 100, 101, 106, 189, 181, 188, 225H and 227 (page 41, lines 13-15).

It would have been obvious to use the mutations taught by Whitcomb in Nijhuis' method. One would have been motivated to incorporate Whitcomb's additional mutations into Nijhuis' method because Nijhuis suggests that there is a relationship between viral replicative capacity and phenotypic resistance (page 27, column 1, second full paragraph). Even in the claims that do not recite positions 103 or 236 (or "not P236L"), it would have been obvious to look for the mutations cited in Whitcomb for the purpose of determining a likelihood of impaired replication capacity as taught by Nijhuis. Nijhuis states, "the mutations associated with the emergence of drug resistance may decrease the intrinsic capacity of the virus to replicate efficiently", page 23, second column, first paragraph. Nijhuis cites several examples including resistance to zidovudine wherein the virus harbors a single amino acid change or a combination of substitutions that have reduced replication capacity compared with the wild type (Table 1).

One would have had a reasonable expectation of success that the detection of other mutations such as those taught by Whitcomb would have been predictive of viral fitness because some of the mutations are the same (K103N, P236L, for example) as those that are associated with both NNRTI resistance and viral fitness. Recall that the claims only require an "increased likelihood of having impaired replication capacity". An increased likelihood of impaired replication capacity associated with the mutations of Whitcomb is not absolute, not necessary and not sufficient (specification, page 10, lines 30-34). Given this low threshold for meeting the

claim limitations, one would have had a reasonable expectation of success that the mutations taught by Whitcomb in combination with Nijhuis' teachings would have led one of ordinary skill in the art to expect an increased likelihood of having impaired replication capacity in a virus with the disclosed mutations.

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention.

Conclusion

4. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off,. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

/Stacy B. Chen/ 5-12-2008
Primary Examiner, Art Unit 1648